REMARKS

Claims 1, 3, 5-8, 11-21, 24-49 are currently pending in this application. Claims 13-15 and 24-45 stand withdrawn as being drawn to a non-elected invention. Thus, claims 1, 3, 5-8, 11, 12,16-21, and 46-49 are under consideration. Claims 1, 7, 46, and 48 are amended herein. Support for these amendments is found generally in the specification; for example, support is found in the specification at Page 2, paragraph [0039] and Page 3, paragraph [0055]. Thus, it is believed that no new matter has been entered.

Objection

The Examiner objected to claim 48 due to an informality. Specifically, the Examiner asserted that claim 48 contains a typographical error in line 1 (the _level).

Claim 48 has been amended herein to correct the typographical error. Additionally, claim 7 has also been amended herein to correct a similar typographical error. Accordingly, the Examiner's objection to claim 48 is believed to be overcome.

Rejections - 35 U.S.C. §103

The Examiner maintained his rejection of claims 1, 3, 5, 16, 17, 19 and 20 under 35 U.S.C. §103(a) as being unpatentable over Togawa et al. (2002 Am. J. Phsiol. Gastrointestinal Liver Physiol. 282:G187-G195) in view of Hart et al. (2003 J. Clin. Gastroenterology 36:111-9). The Examiner also applied this rejection to previously added claim 46. Specifically, the Examiner asserted that Togawa et al. teach a method of determining the efficacy of lactoferrin treatment of animals with experimentally induced inflammatory bowel disease by comparing levels of anti-inflammatory cytokines and pro-inflammatory cytokines in TNBS-administered rats receiving lactoferrin. The Examiner also asserted that Hart et al. teach the efficacy of probiotics in the treatment of an inflammatory bowel disease.

The Examiner also maintained his rejection of claims 18 and 21 under 35 U.S.C. §103(a) as being unpatentable over Togawa et al. and Hart et al. as applied to claims 1, 17, and 20 in view of Vignali et al. (cited in previous Office Action). The Examiner narrowly cited Vignali et al. for teaching a method of measuring levels of at least one anti-inflammatory cytokine and at least one

pro-inflammatory cytokine in a biological sample by multiplexed ELISA's using coded microspheres coupled with a flow cytometer detection system.

The Examiner maintained his rejection of claims 6-8 under 35 U.S.C. §103(a) as being unpatentable over Togawa et al. and Hart et al. as applied to claim 1 and previously added claim 46 in view of Blumberg et al. (1999 Current Opinion in Immunology 11:648-656). The Examiner also applied this rejection to previously added claims 47-49. The Examiner asserted that Blumberg et al. teach immune responses uniquely involved in inflammatory bowel disease pathogenesis and note the importance of balance of pro-inflammatory cytokines such as IFN-γ, TNF, and IL-12, and anti-inflammatory cytokines such as IL-10 and TGF-β.

Finally, the Examiner maintained his rejection of claims 11 and 12 under 35 U.S.C. §103(a) as being unpatentable over Togawa et al. and Hart et al. as applied to claim 1 in view of Bing et al. (1998 World J Gastroenterology 4:252-255). Specifically, the Examiner narrowly cited Bing et al. for teaching measuring cytokine levels produced by peripheral blood mononuclear cells.

Applicants respectfully traverse these assertions.

Independent claims 1 and 46 recite, *inter alia*, a method of determining the efficacy of a probiotic as a treatment of ***irritable bowel syndrome*** wherein an increase in the ratio of levels of anti-inflammatory cytokine to pro-inflammatory cytokine is indicative of the efficacy of said treatment for ***irritable bowel syndrome*** and wherein no change or a decrease in the ratio of the levels of anti-inflammatory to pro-inflammatory cytokine is indicative of lack of efficacy of said treatment for ***irritable bowel syndrome*** (emphasis added). Support for these amendments is found generally in the specification. For example, the specification provides that, "[a]s used herein, "inflammatory diseases of the bowel" include "irritable bowel syndrome–IBS," (*see* page 2, paragraph [0039]), and also provides that, "[p]referably, the method herein is used to determine the efficacy of treatments for irritable bowel syndrome." (*See* Page 3, paragraph [0055]. Thus it is believed that no new matter has been entered.

Applicants submit that Togawa et al. and/or Hart et al. fail to disclose or suggest the limitations recited in independent claims 1 and 46. Specifically, Applicants submit that Togawa et al. and/or Hart et al., either singularly or in combination, not only fail to teach or suggest

determining a ratio of the level of at least one anti-inflammatory cytokine to the level of at least one pro-inflammatory cytokine, but also fail to teach or suggest a method of determining the efficacy of a probiotic as a treatment of ***irritable bowel syndrome*** as recited in claims 1 and 46. Additionally, as acknowledged by the Examiner, Togawa et al. and Hart et al. are directed to the treatment of ***inflammatory bowel disease***, in contrast to ***irritable bowel syndrome***. Thus, Applicants respectfully request the withdrawal of the rejection of independent claims 1 and 46 under 35 U.S.C. § 103(a). Additionally, as claims 3, 5-8, 11, 12,16-21, and 47-49 depend from independent claims 1 or 46, Applicants also respectfully request the withdrawal of the rejection of these claims under 35 U.S.C. § 103(a).

Further, Applicants maintain that independent claims 1 and 46 are patentable over Togawa et al. in view of Hart et al. In general, to establish a prima facie case of obviousness, the Examiner must show, by reasoning or evidence, one or more of the following rationales: (A) Combining prior art elements according to known methods to yield predictable results; (B) Simple substitution of one known element for another to obtain predictable results; (C) Use of known technique to improve similar devices (methods, or products) in the same way; (D) Applying a known technique to a known device (method, or product) ready for improvement to yield predictable results; (E) "*Obvious to try*" - choosing from a finite number of identified, predictable solutions, with a reasonable expectation of success; (F) Known work in one field of endeavor may prompt variations of it for use in either the same field or a different one based on design incentives or other market forces if the variations are predictable to one of ordinary skill in the art; or (G) Some teaching, suggestion, or motivation in the prior art that would have led one of ordinary skill to modify the prior art reference or to combine prior art reference teachings to arrive at the claimed invention. See MPEP §2143 and *KSR International Co. v. Teleflex Inc.*, 127 S.Ct. 1727, 167 L.Ed.2d 705, 82 USPQ2d 1385 (2007). The Examiner has failed to establish any of the rationales set forth above to support the conclusion of obviousness.

A rejection based on §103 clearly must rest on a factual basis, and these facts must be interpreted without hindsight reconstruction of the invention from the prior art. *In re Warner*, 154 USPQ 173, 178 (CCPA 1967). The Examiner may *not*, because he may doubt that the invention is

patentable, resort to speculation, unfounded assumptions, or hindsight reconstruction to supply deficiencies in his required factual basis. *Id.*

Independent claims 1 and 46 recite, *inter alia*, a method of determining the efficacy of a probiotic as a treatment of irritable bowel syndrome comprising: (a) measuring the level of at least one anti-inflammatory cytokine and at least one pro-inflammatory cytokine, (b) determining the ratio of the level of the at least one anti-inflammatory cytokine to the level of the at least one pro-inflammatory cytokine, administering said treatment, (c) measuring the level of the at least one anti-inflammatory cytokine and the at least one pro-inflammatory cytokine, and (d) determining the ratio of the level of the at least one anti-inflammatory cytokine to the level of the at least one pro-inflammatory cytokine, wherein an increase in the ratio of the levels of anti-inflammatory cytokine to pro-inflammatory cytokine following the administration of said treatment is indicative of the efficacy of said treatment, and no change or a decrease in the ratio of the levels of anti-inflammatory to pro-inflammatory cytokine is indicative of lack of efficacy of said treatment.

Determining the Ratio

The Examiner ***admitted*** that ***neither Togawa et al. nor Hart et al. teach or suggest determining the ratio*** of the level of ***at least one anti-inflammatory cytokine to the level of at least one pro-inflammatory cytokine before and after treatment***. However, the Examiner still concluded that it would have been obvious to one of ordinary skill in the art at the time the invention was made to determine the ratio of the level of at least one anti-inflammatory cytokine to the level of at least one pro-inflammatory cytokine before and after treatment, stating that one of ordinary skill in the art would have been motivated to compute ratios as a convenient way of determining shifts in the patterns of cytokine levels. Moreover, the Examiner asserted that one would reasonably expect success because methods of measuring cytokine levels in biological samples is well known in the art, and is taught by Togawa et al. Applicants respectfully traverse the Examiner's assertions.

Firstly, Applicants submit that Togawa et al. and Hart et al. are completely void of any teaching or suggestion of determining the efficacy of probiotics in the treatment of irritable bowel syndrome by determining the ratio of the level of at least one anti-inflammatory cytokine to the level of at least one pro-inflammatory cytokine before and after treatment. Moreover, Applicants submit that Togawa et al. and Hart et al., singularly or in combination, fail to provide any teaching,

suggestion, or motivation to determine the ratio of the level of at least one anti-inflammatory cytokine to the level of at least one pro-inflammatory cytokine before and after treatment with a probiotic.

Secondly, Applicants submit that determining the level of at least one pro-inflammatory cytokine before and after treatment with a probiotic yields unexpected results with regard to determining the efficacy of a probiotic as a treatment of irritable bowel syndrome in mammals *in vivo*. "Rebuttal evidence may include evidence of 'secondary considerations.'" *Graham v. John Deere Co.*, 383 U.S. at 17, 148 USPQ at 467. Additionally, the MPEP provides that, "'secondary considerations,' may include evidence of commercial success, long-felt but unsolved needs, failure of others, and unexpected results," *see* MPEP §2141, and also provides that, "[t]he evidence ***may be included in the specification as filed***." *See* MPEP § 2141, emphasis added. Moreover, the MPEP provides that, "[e]vidence that the compound or composition possesses superior and unexpected properties in one of a spectrum of common properties can be sufficient to rebut a *prima facie* case of obviousness." *See* MPEP §2145.

As previously discussed, independent claims 1 and 46 recite, *inter alia*, determining the ratio of the level of at least one anti-inflammatory cytokine to the level of at least one pro-inflammatory cytokine before and after treatment with a probiotic, wherein an increase in the ratio of the levels of anti-inflammatory cytokine to pro-inflammatory cytokine following the administration of the treatment is indicative of the efficacy of the treatment for irritable bowel syndrome. The ***specification*** of the present invention provides that, "[i]t has surprisingly been found that by increasing the ratios described herein the symptoms of inflammatory diseases of the bowel can be alleviated." (*See* Page 6, ¶ 0076). The ***specification*** of the present invention also provides that, "[w]ithout wishing to be bound by theory, it is believed that the specific ratios described herein are pivotal to the progression or remission of inflammatory diseases of the bowel." (*See* Page 6, ¶ 0076).

Thus, Applicants submit that the determination of a ratio of the level of at least one anti-inflammatory cytokine to the level of at least one pro-inflammatory cytokine before and after treatment with a probiotic yielded unexpected results with regard to determining the efficacy of a probiotic. As a result, Applicants submit that it would not have been obvious to one of ordinary skill

in the art at the time the invention was made to determine the ratio of the level of at least one anti-inflammatory cytokine to the level of at least one pro-inflammatory cytokine before and after treatment with a probiotic.

Determining the Efficacy of a Probiotic

Also with regard to independent claims 1 and 46, the Examiner admitted that Togawa et al. fail to disclose a method of determining the efficacy of a probiotic as a treatment of inflammatory bowel disease in mammals. However, the Examiner still concluded that it would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute a probiotic treatment, as taught by Hart et al., with the lactoferrin treatment disclosed in Togawa et al. More particularly, the Examiner stated that Hart et al. disclose the efficacy of probiotics in the maintenance of remission of ulcerative colitis and in the treatment of Crohn's disease and, as a result, it would have been obvious to substitute a method of determining the efficacy of a probiotic treatment of irritable bowel syndrome in mammals for a method of determining the efficacy of lactoferrin treatment of inflammatory diseases of the bowel in mammals. Applicants respectfully traverse the Examiner's assertions.

Firstly, Applicants submit that neither Togawa et al. nor Hart et al., either singularly or in combination, teach or suggest a method of determining the efficacy of a probiotic treatment as recited in independent claim 1. More particularly, Applicants submit that neither Togawa et al. nor Hart et al., either singularly or in combination, teach or suggest a method of determining the efficacy of a probiotic by measuring the levels of at least one anti-inflammatory cytokine to at least one pro-inflammatory cytokine before and after treatment with a probiotic and determining the ratio of at least one anti-inflammatory cytokine to at least one pro-inflammatory cytokine before and after treatment with a probiotic.

Secondly, Applicants submit that it would not have been obvious to one of ordinary skill in the art at the time the invention was made to substitute a method of determining the efficacy of a probiotic treatment of irritable bowel syndrome in mammals as claimed for a method of determining the efficacy of lactoferrin treatment of inflammatory diseases of the bowel in mammals. The specification of the present invention provides that, "[t]he control of inflammatory diseases is exerted at a number of levels," (*see* Page 1, ¶ 0010), and further provides that, "[t]he controlling

factors include hormones, prostaglandins, reactive oxygen and nitrogen intermediates, leukotrienes and cytokines." (*See* Page 1, ¶ 0010). Moreover, the specification of the present invention provides that the very nature of inflammatory diseases of the bowel means that screening and measuring the efficacy of potential treatments in human subjects is very difficult. (*See* Page 1, ¶ 0008).

As a result, Applicants submit that determining the efficacy of a probiotic as a treatment of irritable bowel syndrome in mammals *in vivo* is an unpredictable art. Thus, because of the difficulties associated with determining the efficacy of potential treatments of irritable bowel syndrome in an unpredictable art, Applicants further submit that it would not have been obvious to one of ordinary skill in the art to ***randomly*** substitute, without more, a method of determining the efficacy of a probiotic treatment for irritable bowel syndrome for a method of determining the efficacy of lactoferrin treatment of inflammatory diseases of the bowel from the teachings of Togawa et al. in view of Hart et al.

Hindsight Reconstruction

Moreover, since neither Togawa et al. nor Hart et al., singularly or in combination, teach or suggest: (1) determining the ratio of at least one anti-inflammatory cytokine to at least one pro-inflammatory cytokine before and after treatment with a probiotic; or (2) substituting a probiotic treatment for a lactoferrin treatment, Applicants are left with the only conclusion that the Examiner has improperly used their application as a road map through impermissible hindsight reconstruction. The motivations the Examiner provided for his asserted combination include: (1) that it would have been obvious to one of ordinary skill in the art at the time the invention was made to determine the ratio of the level of at least one anti-inflammatory cytokine to the level of at least one pro-inflammatory cytokine before and after treatment, because one of ordinary skill in the art would have been motivated to compute ratios as a convenient way of determining shifts in the patterns of cytokine levels; and (2) that it would have been obvious to substitute a method of determining the efficacy of a probiotic treatment of inflammatory diseases of the bowel in mammals for a method of determining the efficacy of lactoferrin treatment of inflammatory diseases of the bowel in mammals based upon the disclosure in Hart et al. regarding the efficacy of probiotics in the maintenance of remission of ulcerative colitis and in the treatment of Crohn's disease.

Firstly, as previously discussed, Applicants submit that due to the unexpected results yielded from the determination of the ratio of the level of at least one anti-inflammatory cytokine to the level of at least one pro-inflammatory cytokine before and after treatment with a probiotic, it would not have been obvious to one of ordinary skill in the art to determine the ratio of the level of at least one anti-inflammatory cytokine to the level of at least one pro-inflammatory cytokine before and after treatment with a probiotic. Secondly, as previously discussed, Applicants submit that because of the difficulties associated with determining the efficacy of potential treatments of irritable bowel syndrome in an unpredictable art, it would not have been obvious to one of ordinary skill in the art to substitute a method of determining the efficacy of a probiotic treatment of irritable bowel syndrome for a method of determining the efficacy of lactoferrin treatment of inflammatory diseases of the bowel from the teachings of Togawa et al. in view of Hart et al.

In contrast, the specification of the present invention provides that, "[w]ithout wishing to be bound by theory, it is believed that the specific ratios described herein are pivotal to the progression or remission of inflammatory diseases of the bowel." (*See* Page 6, ¶ 0076). The specification also provides that the treatments may comprise probiotic compositions. (*See* Page 3, ¶ 0056). Additionally, the specification further provides that the levels of at least one anti-inflammatory cytokine and at least one pro-inflammatory cytokine are measured. (*See* Page 5, ¶ 0073). Thus, Applicants contend that the Examiner's combination of Togawa et al. and Hart et al. is a product of impermissible hindsight reconstruction.

As set forth above, none of the references, singularly or in combination, makes a distinction, suggestion, or recognition that: (1) the ratio of at least one anti-inflammatory cytokine to at least one pro-inflammatory cytokine should be determined before and after treatment with a probiotic; or (2) a probiotic treatment should be substituted for a lactoferrin treatment. Moreover, Applicants submit that determining the efficacy of a probiotic as a treatment of irritable bowel syndrome in mammals *in vivo* is an unpredictable art. Therefore, without more, Applicants submit that one of ordinary skill in the art would not have been taught or motivated to: (1) determine the ratio of the level of at least one anti-inflammatory cytokine to the level of at least one pro-inflammatory cytokine before and after treatment; or (2) combine a probiotic treatment with a method of determining the efficacy of a treatment of irritable bowel

syndrome in mammals. As a result, Applicants respectfully request the withdrawal of the rejection of claims 1 and 46 under 35 U.S.C. §103. As claims 3, 5-8, 11, 12, 16-21, and 47-49 depend from independent claims 1 or 46, Applicants also respectfully request the withdrawal of the rejection of these claims under 35 U.S.C. §103.

CONCLUSION

It is believed that the above represents a complete response to the Office Action dated August 27, 2010. In light of the foregoing, Applicants respectfully submit that the application is in condition for allowance. The Examiner is encouraged to contact the undersigned to resolve efficiently any formal matters or to discuss any aspects of the application or of this response. Otherwise, early notification of allowable subject matter is respectfully solicited.

Respectfully submitted,
DINSMORE & SHOHL LLP

By: /Hallie W. Wherley/
Hallie W. Wherley
Registration No. 66,800

Fifth Third Center
One South Main Street, Suite 1300
Dayton, Ohio 45402-2023
Telephone: (937) 449-6400
Facsimile: (937) 449-6405

HWW